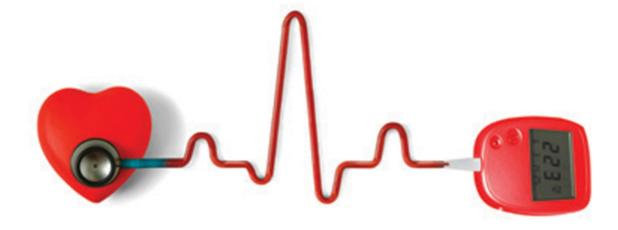
Prevention of Cardiovascular Disease in the Patient with Diabetes

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Disclosures

Drs. Anderson and Nawarskas have received contract funding through the New Mexico Department of Health Heart Disease and Stroke Prevention Program.

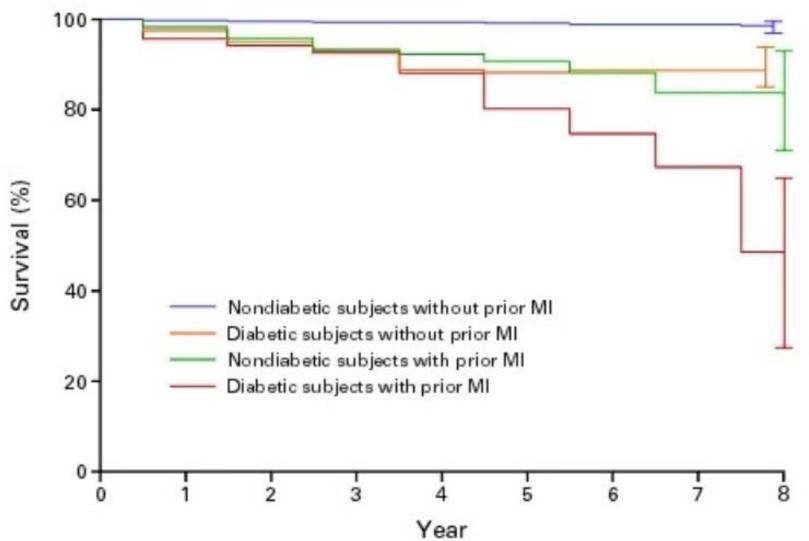
Learning Objectives

Following this presentation, the participants will be able to:

- 1. Describe the role of hypertension management in patients with diabetes for the prevention of cardiovascular disease.
- 2. Describe the role of cholesterol management in patients with diabetes for the prevention of cardiovascular disease.
- 3. Discuss the controversies surrounding the use of aspirin for the prevention of cardiovascular disease in the patient with diabetes.
- 4. Summarize the results of recent clinical trials investigating the effects of glucose-lowering agents on cardiovascular disease.



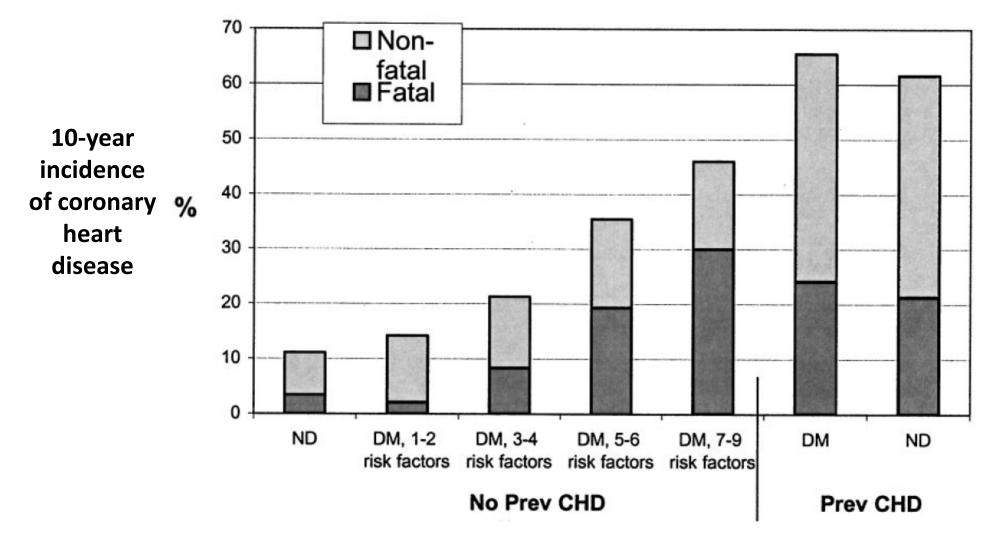
Diabetes has been considered a "cardiovascular risk equivalent"



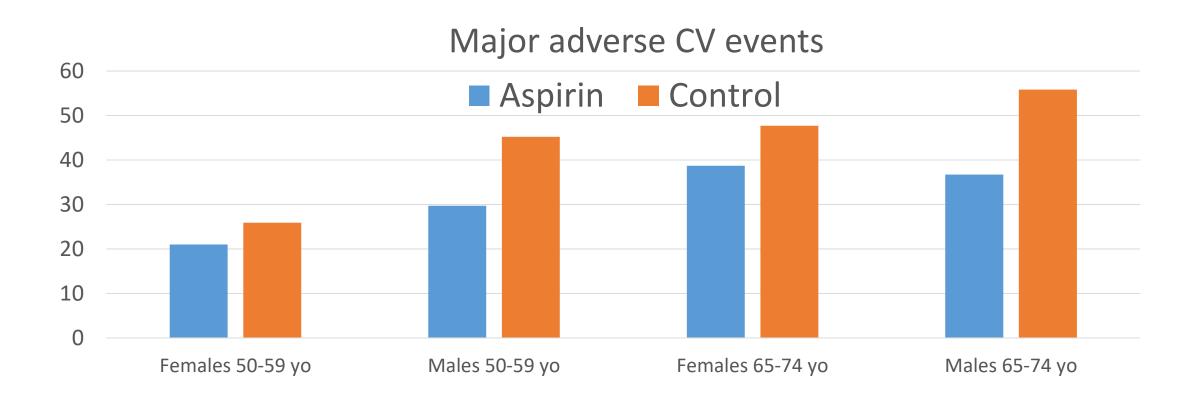
Haffner et al. N Engl J Med 1998;339:229-234.



"Cardiovascular risk equivalent" may only apply to patients with diabetes and at least 5 risk factors



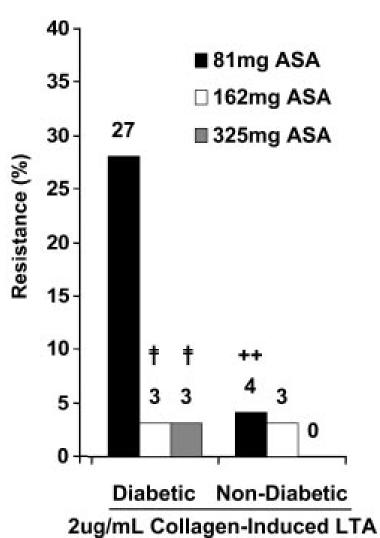
For secondary prevention, the risk of a recurrent CV event is so high that the benefits of aspirin outweigh the risks.



Pathophysiologically, aspirin therapy makes sense for patients with diabetes

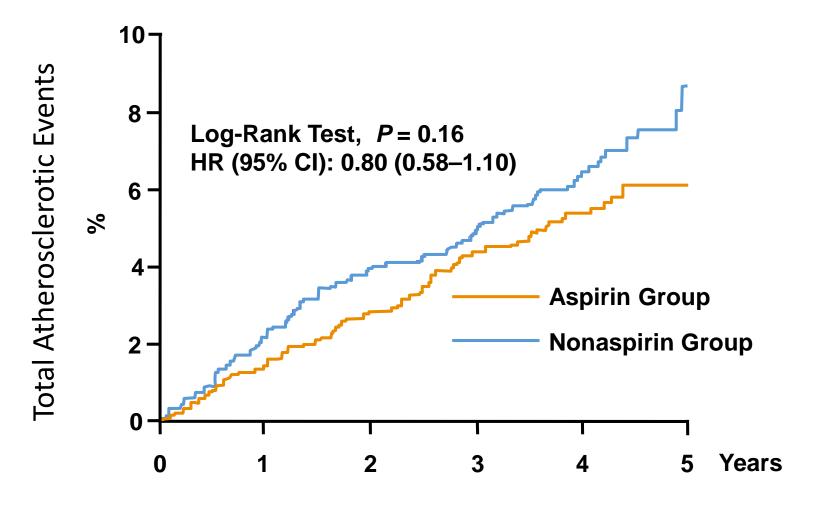
Patient with diabetes have increased:

- Risk of CV disease
- Platelet aggregability
- Thromboxane release from platelets
- Prevalance of aspirin resistance

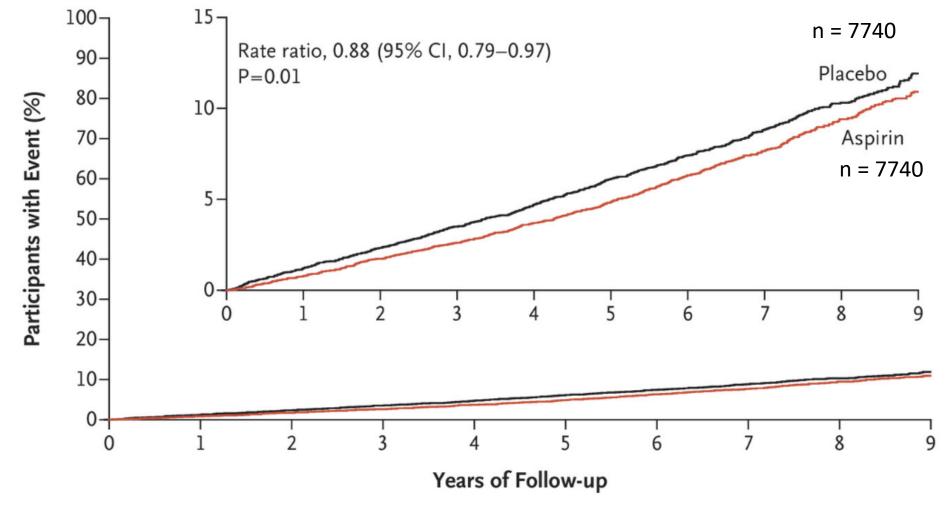


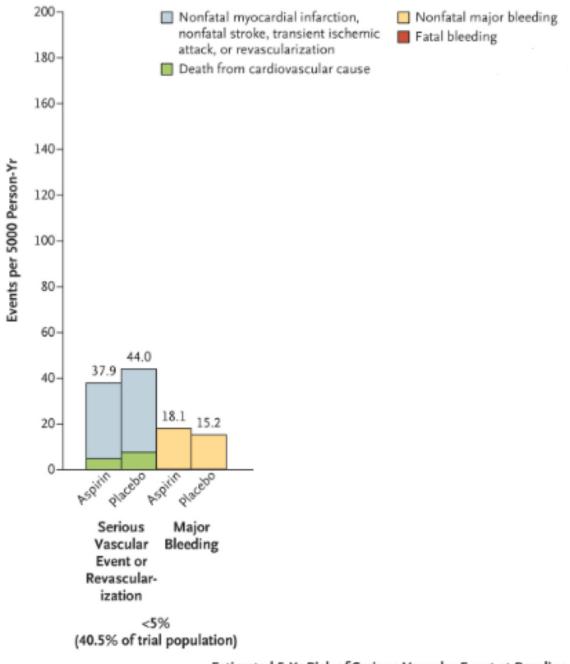


The JPAD Study demonstrated that low-dose aspirin as primary prevention neither reduced CV events nor increased bleeding in patients with diabetes

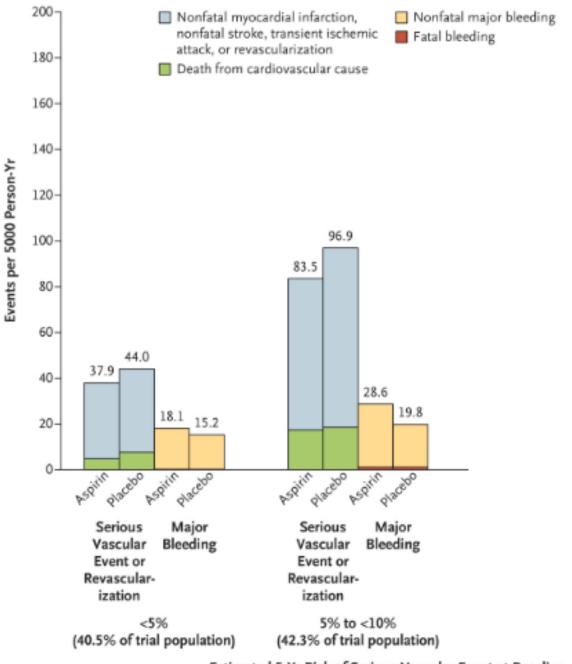


...but the larger ASPECT trial did show some benefit with low-dose aspirin in preventing CV events in patients with diabetes



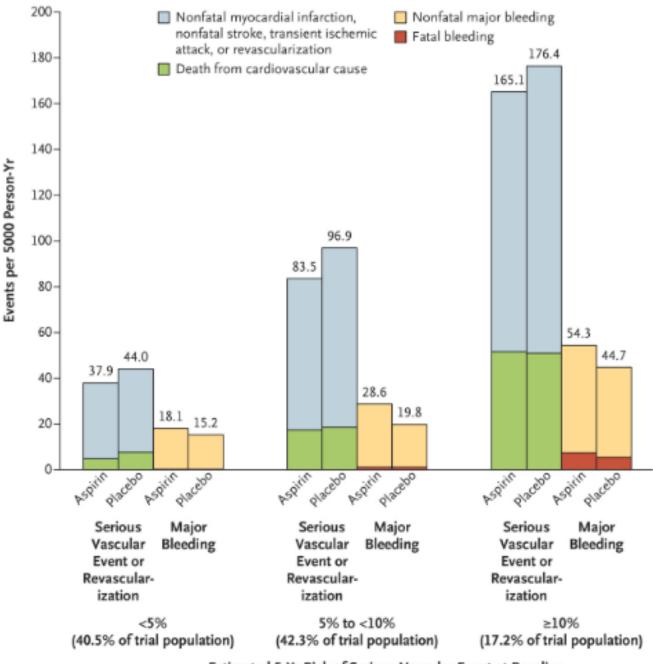


ASCEND Study Group. N Engl J Med 2018;379:1529-1539.



Estimated 5-Yr Risk of Serious Vascular Event at Baseline

ASCEND Study Group. N Engl J Med 2018;379:1529-1539.



...albeit at a higher risk of bleeding

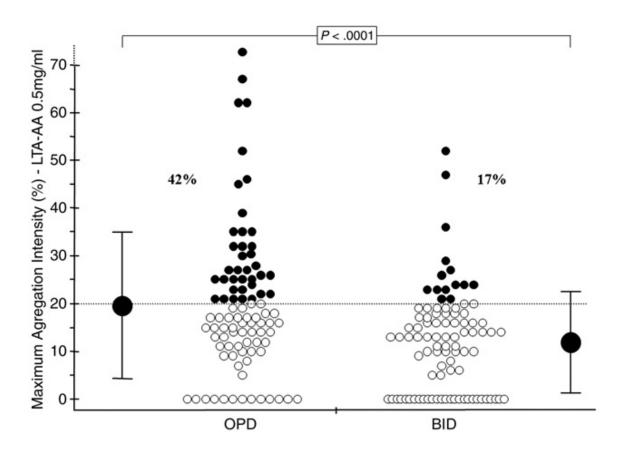
NNT = 91

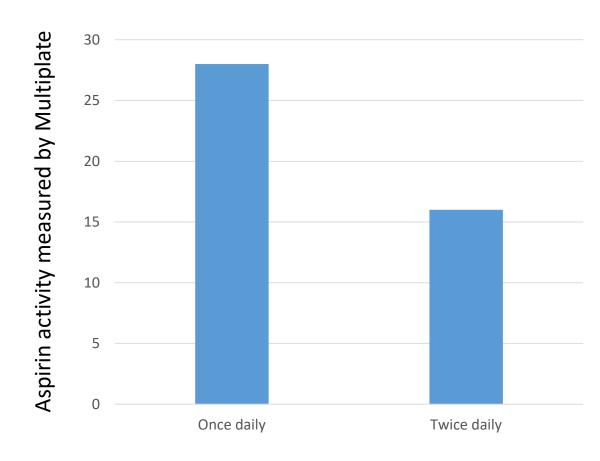
NNH = 112

ASCEND Study Group. N Engl J Med 2018;379:1529-1539.

Estimated 5-Yr Risk of Serious Vascular Event at Baseline

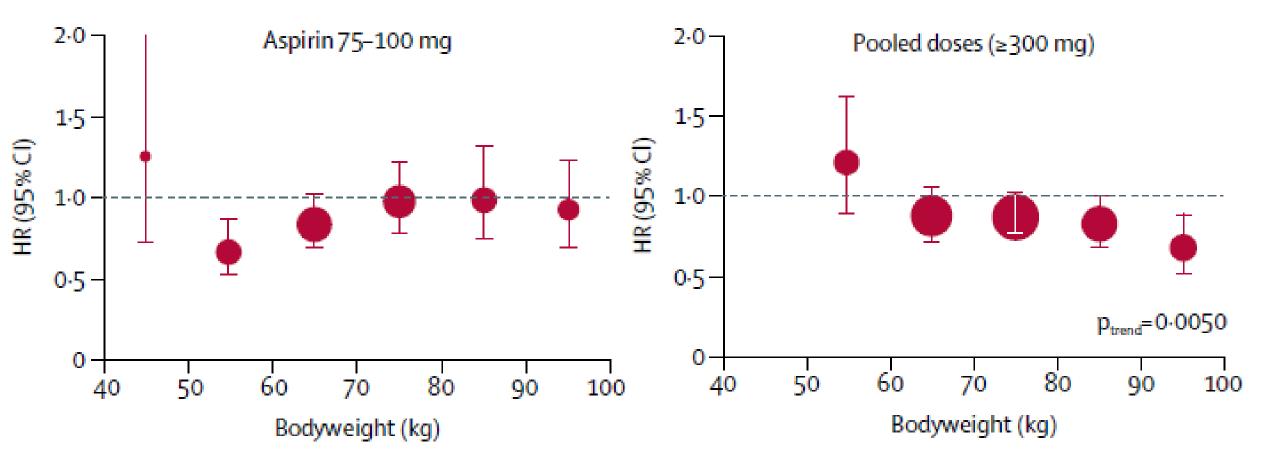
Patients with diabetes may respond better to twice daily versus once daily aspirin





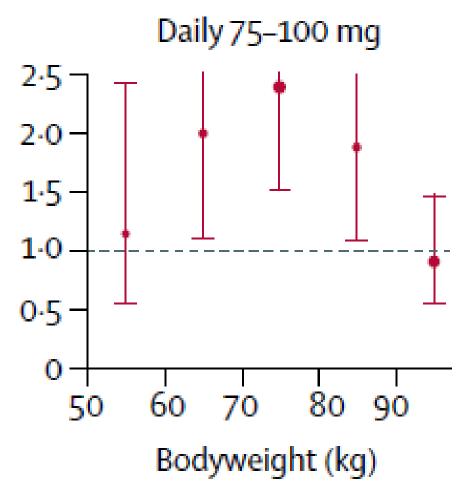
Low dose aspirin (75–100 mg/d) may only be effective in preventing vascular events in patients weighing < 70 kg

All cardiovascular events



Dillinger J-G et al. *Am Heart J* 2012;164:600-606.e1

The bleeding risk of low dose aspirin (75–100 mg/d) may only be lost in patients weighing \geq 90 kg



STANDARDS OF MEDICAL CARE IN DIABETES ASSOCIATION

Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased CV risk.

 This includes most individuals with diabetes ≥ 50 years of age who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding.

Consequences of High Blood Pressure



High blood pressure (HBP) can injure or kill you. when high blood pressure is uncontrolled, it can lead to:

STROKE

HBP damages arteries that burst or clog more easily.

77% of people who have a first stroke have HBP.

HBP increases your stroke risk by four to six times.

HEART FAILURE

HBP can cause the heart to enlarge and fail to supply blood to the body.

75% of people with congestive heart failure have HBP.

ERECTILE DYSFUNCTION

HBP leads to erectile dysfunction because of reduced blood flow throughout the body.

Did You Know?

- At 50, total life expectancy is five years longer for people with normal blood pressure.
- The estimated cost of HBP in 2010 (the most-recent statistics available) is \$46.4 billion.

VISION LOSS

HBP can strain the vessels in the eyes.

HEART ATTACK

HBP damages arteries that can become blocked.

69% of people who have a first heart attack have HBP.

KIDNEY DISEASE/FAILURE

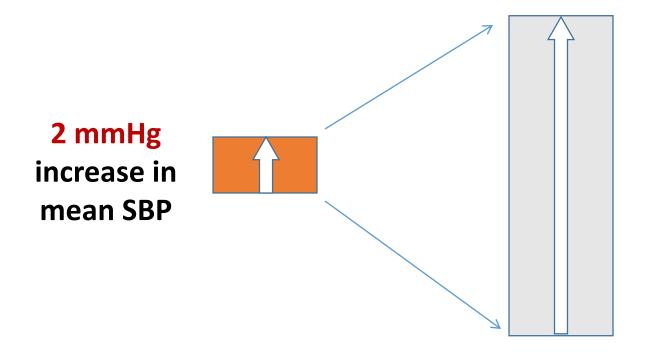
HBP can cause arteries around the kidneys to narrow, weaken or harden so the kidneys lose their ability to filter blood.

HBP is the second-leading cause of kidney failure

These conditions can happen over several years, but they can be prevented by controlling blood pressure.

Check. [™] Change. Control.™

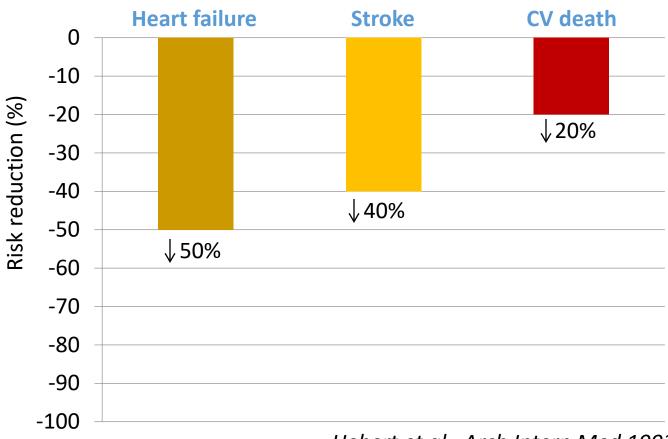
BP reductions as small as 2 mmHg may reduce the risk of CV events by up to 10%



7% increase in risk of ischemic heart disease mortality

10% increase in risk of stroke mortality

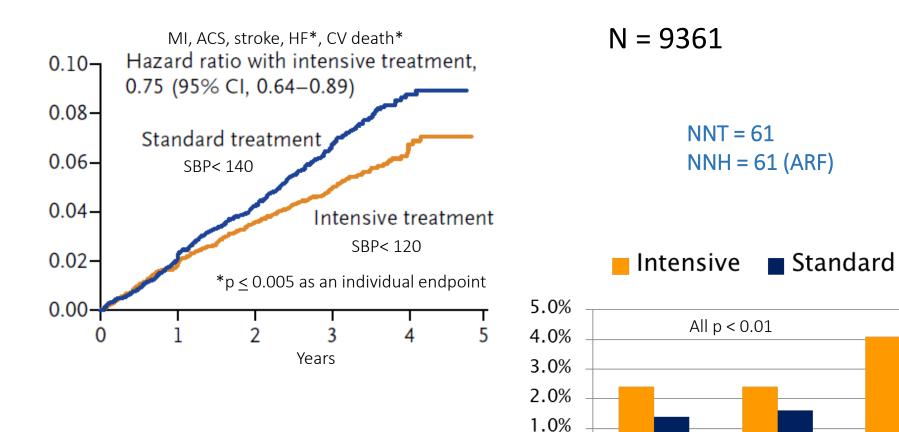
Hypertension treatment reduces major adverse cardiovascular events



Hebert et al. Arch Intern Med 1993; 153:578-81. Moser et al. J Am Coll Cariol 1996;27:1214-8.



SPRINT Results: Lower is Better (?)





Hypotension Hypokalemia Acute renal

failure

0.0%

BP goal is now <130/80 mmHg for most patients ...except those with diabetes?

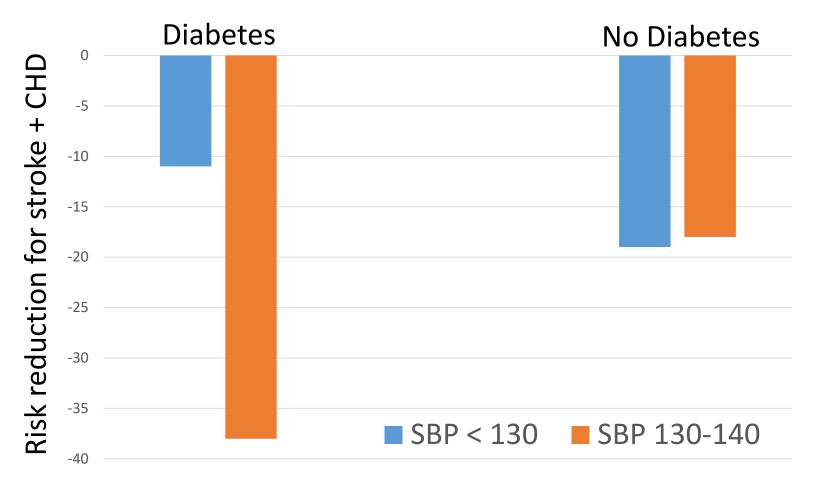
STANDARDS OF MEDICAL CARE IN DIABETES ASSOCIATION

"Most patients with diabetes and hypertension should be treated to BP goal of <140/90 mmHg. Lower targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden."

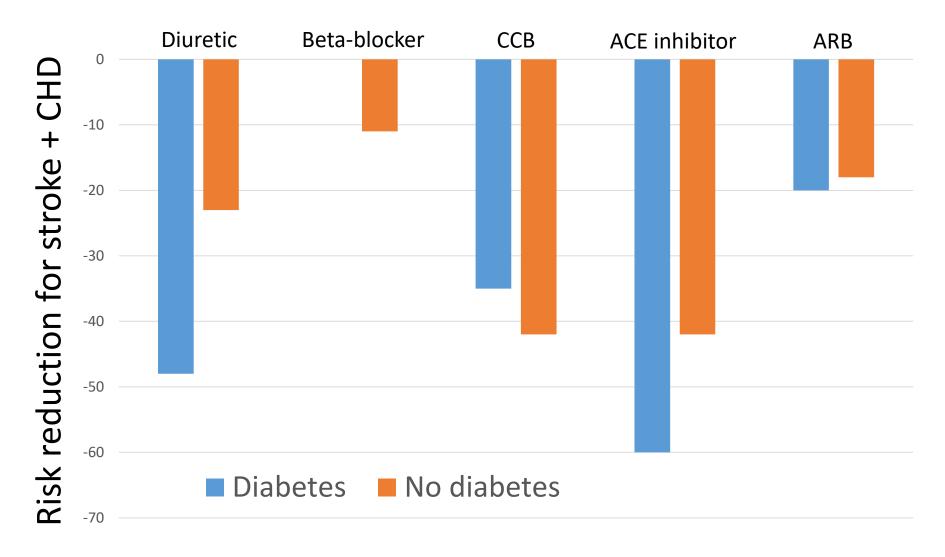
Diabetes Care 2018;41(Suppl. 1):S86-S104.

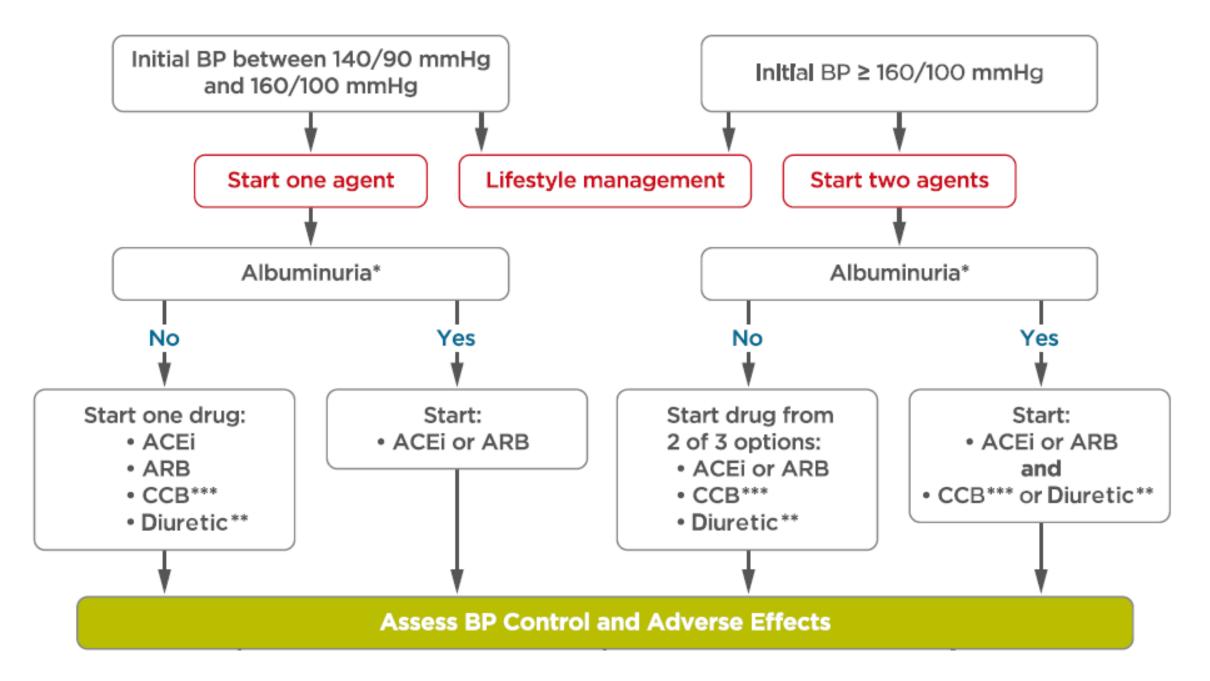
Whelton, et al. 2017 ACC/AHA High Blood Pressure Guideline. Hypertension; Nov. 13, 2017

There is little or no further benefit in lowering SBP below 130 mmHg in patients with diabetes, in contrast to patients without diabetes.

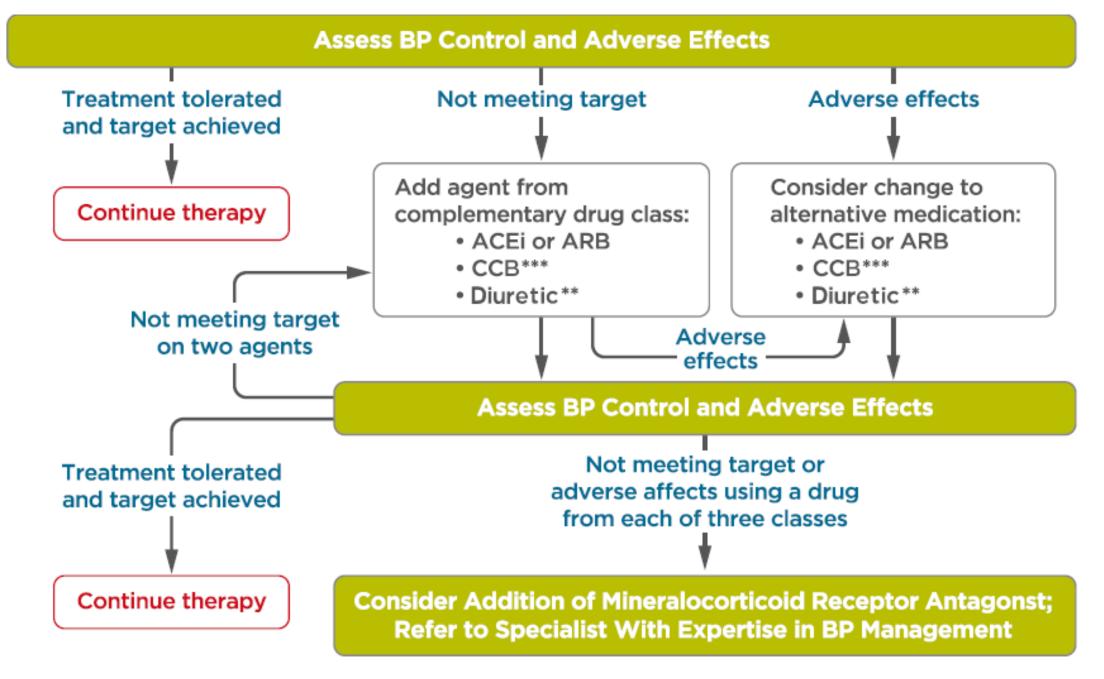


Many antihypertensives are effective for patients with diabetes, ACE inhibitors perhaps more than others





Diabetes Care 2018;41(Suppl. 1):S86-S104.

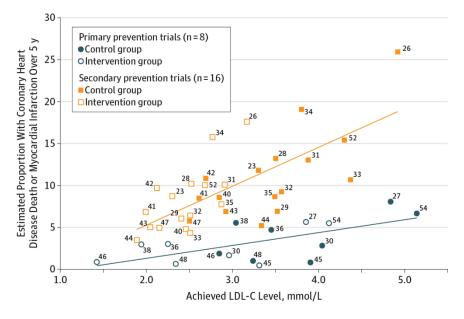


Cholesterol-lowering and CV Disease

LDL-lowering and CV disease risk

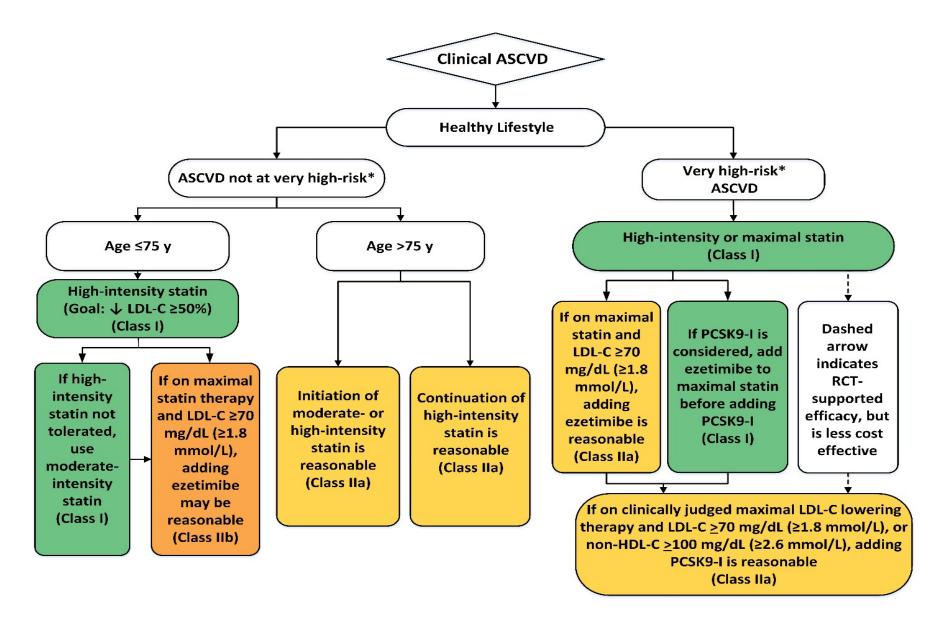
- A 1 mmol/L (38.7 mg/dL) reduction of LDL = a 21% reduction in ASCVD events
- Or a 1% reduction in LDL = a 1% reduction in risk of ASCVD

J Am Coll Cardiol. 2014;64:485-94.



Association Between Achieved Low-Density Lipoprotein Cholesterol (LDL-C) and Major Coronary Event Rates From 24 Trials of Established Interventions That Lower LDL-C Predominantly Through Upregulation of LDL Receptor Expression. Levels of LDL-C are expressed as mean or median depending on what was reported in the trial. The solid lines are from meta-regression. To convert LDL-C from mmol/L to mg/dL, divide by 0.0259.

2018 ACC-AHA Cholesterol Guidelines



Intensity of Statin Therapy*

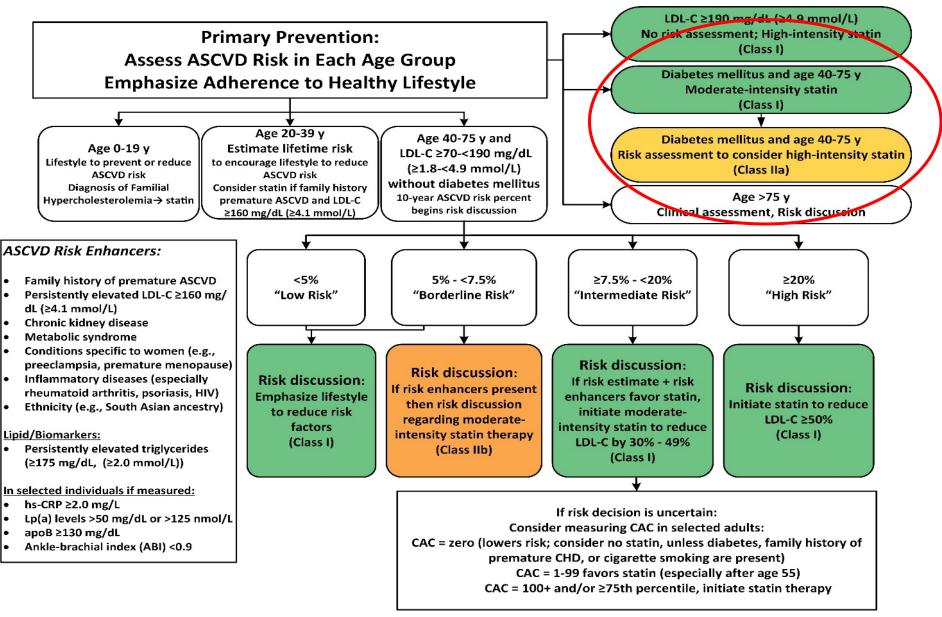
High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Daily dose lowers LDL–C by approximately > 50%	Daily dose lowers LDL–C by approximately 30 to < 50%
Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin 40 mg bid Fluvastatin XL 80 mg Pitavastatin 2–4 mg

Bolded Statins and doses: RCTs demonstrating efficacy Italicized statins and doses are FDA-approved but not tested in RCTs

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL Study. ‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

^{*}Individual responses to statin therapy varied in the RCTs. There might be a biologic basis for a less-than-average response.

2018 ACC-AHA Cholesterol Guidelines



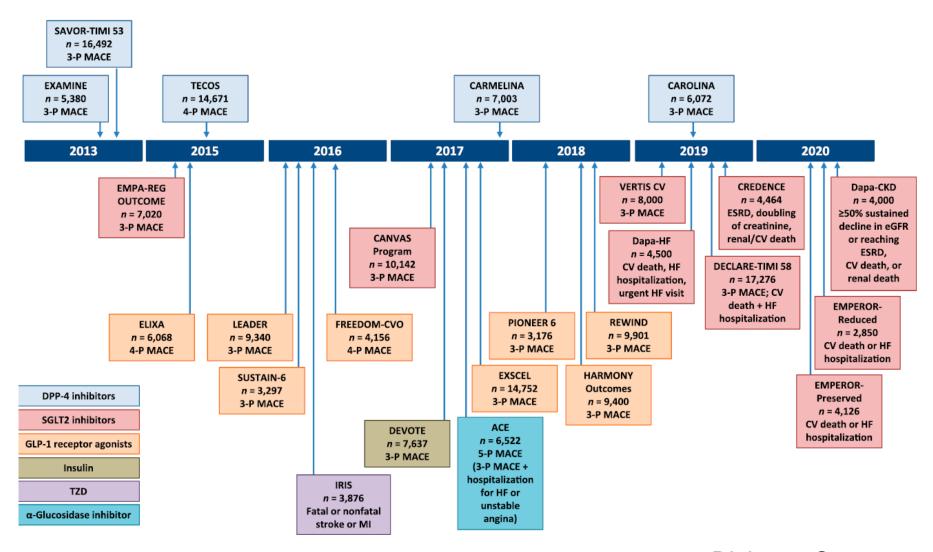
Available at: https://www.acc.org/guidelines/hubs/blood-cholesterol

Diabetes Agents and CV Disease

Diabetes Medication Cardiovascular Outcomes Trials (CVOT): FDA Mandate

- 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
 - Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
 - Some study designs tested for superiority if noninferiority criteria were met
 - Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
 - Some primary endpoints included additional components

Timeline of Major DM CVOT Trials





Sodium-glucose co-transporter 2 inhibitors (SGLT2i)

Trial	Drug	Population	MACE	CV Death	HF Hospitalization
EMPA-REG Outcome	Empagliflozin (Jardiance®)	DM2 & CVD	14% reduction	38% reduction	35% reduction
CANVAS Program	Canagliflozin (Invokana®)	DM2 & CVD or age \geq 50 with \geq 2 CV RFs	14% reduction	13% reduction*	33% reduction
DECLARE-TIMI 58	Dapagliflozin (Farxiga®)	DM2 & CVD or with multiple CV RFs	7% reduction*	2% reduction*	27% reduction

*not statistically significant

FDA approval of SGLT2i

- Empagliflozin is indicated to reduce the risk of CV death in adult patients with DM2 and established CVD.¹
- Canagliflozin is indicated to reduce the risk of MACE in adults with DM2 and established CVD.²

- 1. Jardiance ® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2018.
- 2. Invokana ® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2018.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

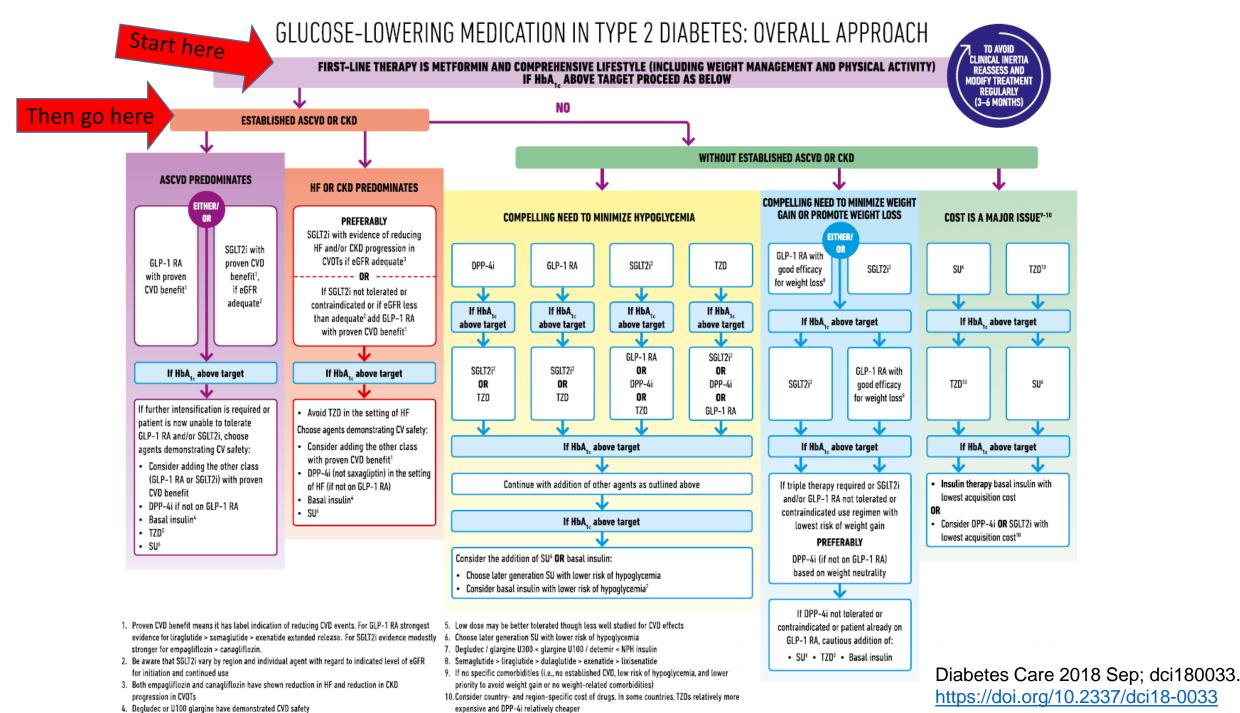
Trial	Drug	Population	MACE	CV Death	HF Hospitalization
LEADER	Liraglutide (Victoza®)	DM2 & CVD, CKD, or HF; or DM2 & \geq 60 with \geq 1 CV RF	13% reduction	22% reduction	13% reduction*
SUSTAIN-6	Semaglutide (Ozempic®)	Same as LEADER	26% reduction	2% reduction*	11% increase*
ELIXA	Lixsenatide (Soliqua®)	DM2 and acute coronary event	No difference	No difference	No difference
EXSCEL	Exenatide (Bydureon®)	DM2 with or without CVD	9% reduction*	12% reduction*	6% reduction*
PIONEER 6**	Semaglutide (oral form)	DM2 & CVD or <u>></u> 60 with <u>></u> 1 CV RF	21% reduction*	51% reduction	Not reported

^{*}not statistically significant
**results not published

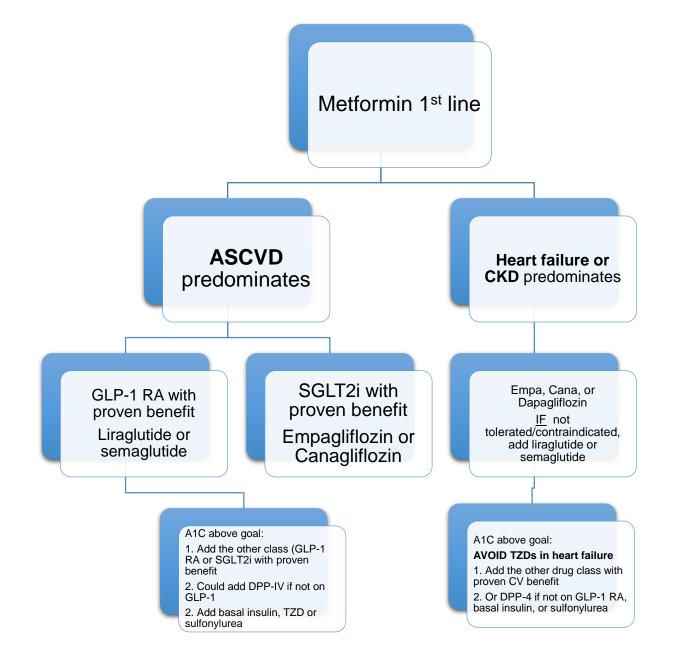
FDA approval of GLP-1 RA

 Liraglutide is indicated to reduce the risk of MACE in adults with DM2 and established CVD.¹





ASCVD or Heart failure or CKD



Reduction of CV Disease

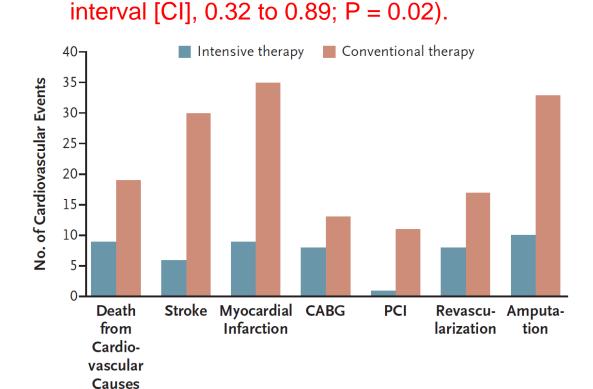
- CV disease risk is elevated in patients with DM
- The best way to prevent CV disease is through multi-factorial risk reduction
 - Use aspirin when appropriate
 - Control blood pressure (ACEIs or ARBs preferred)
 - Control cholesterol (Statins preferred)
 - Control glucose (metformin + agent based on presence of ASCVD, HF, or CKD)
 - Quit smoking
 - Exercise
 - Healthy diet

The Steno-2 Study

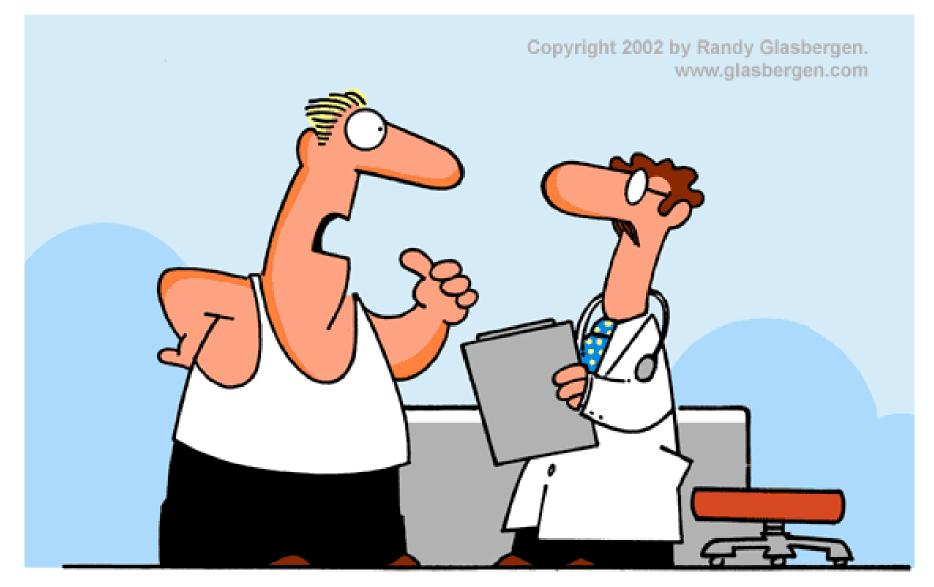
 Intensified multifactorial intervention with tight glucose regulation and the use of renin-angiotensin system blockers, All-cause mortality: HR 0.54, (95% confidence

aspirin, and lipid-lowering agents.

Conventional therapy Intensive therapy P = 0.14P = 0.35P = 0.00580-70-Patients (%) P = 0.27P = 0.3110-Cholesterol **Triglycerides** Systolic Blood Diastolic Blood Glycated Hemoglobin <175 mg/dl <150 mg/dl Pressure Pressure <6.5% <130 mm Hg <80 mm Hg



N Engl J Med 2008:358:580-91.



"I've always been a high achiever, always striving for bigger, faster, greater...and now suddenly I'm expected to settle for *lower* blood pressure and *less* cholesterol?!"

Proper Blood Pressure Measurement in the Clinic and the Home

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Associate Professors of Pharmacy Practice and Internal Medicine

University of New Mexico College of Pharmacy and School of Medicine

Learning objectives

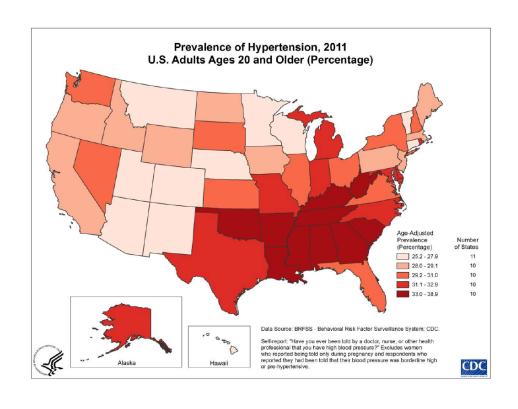
Following this application-based presentation, the participants will be able to:

- Explain the American Heart Association methods for proper blood pressure measurement;
- Review situations and/or actions that would result in inaccurate assessment of blood pressure;
- Demonstrate the proper technique for assessing blood pressure;
- Counsel a patient in the proper technique for self-monitoring blood pressure (SMBP).

Disclosures: Dr. Anderson and Dr. Nawarskas have received contract funding through the New Mexico Department of Health Heart Disease and Stroke Prevention Program.

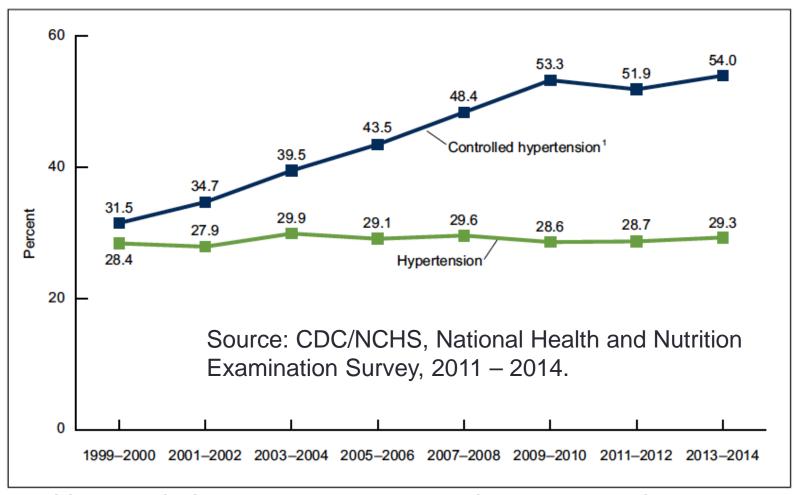
Consequences of HTN

- 70 million adults in the USA have HTN
 - 1 in 5 adults are unaware that they have HTN
- Responsible for 360,000 deaths per year
 - 1,000 deaths per day!
- Indirect and direct costs estimated \$46 Billion



Prevalence and Control of HTN

Figure 5. Age-adjusted trends in hypertension and controlled hypertension among adults aged 18 and over: United States, 1999–2014



Yoon SS, et al. NCHS data brief, no 220. National Center for Health Statistics. 2015.

Blood pressure classification

BP Classification	SBP (mmHg)		DBP (mmHg)
Normal	< 120	and	< 80
Elevated	120 – 129	or	< 80
Stage 1 hypertension	130 – 139	or	80 – 89
Stage 2 hypertension	≥ 140	or	≥ 90
Hypertensive Crisis	≥ 180	or	≥ 120

Assessing Blood Pressure

 The 2017 ACC-AHA High Blood Pressure Guidelines emphasized the importance of measuring blood pressure properly following validated methods

COR	LOE	Recommendation for Accurate Measurement of BP in the Office
1	C-EO	For diagnosis and management of high BP, proper methods are recommended for accurate measurement and documentation of BP.

Arm Position

- > Should be at the level of the right atrium (midpoint of the cuff should be at the midpoint of the sternum)
 - If arm is below, BP will be higher than expected
 - If arm is too high, BP will be lower
 - 2 mmHg for every inch above or below the heart level¹
- > Arm should be supported (relaxed).

Rest period

- > Patient should rest quietly for 5 minutes prior to measurement
 - Anxiety/stress increases BP
 - Recent physical activity increases BP

Posture

- Seated
 - Sitting raises BP by ~ 5 mmHg as compared to the supine position
- > Back should be supported (with chair)
 - Unsupported back increases DBP up to 6 mmHg²
- > Feet should be flat on the ground
 - If dangling, can increase BP
- > Legs should be uncrossed
 - Crossing the legs increased SBP by 2 to 8 mmHg³

- 1. Circulation 2005;111:697-716.
- 2. Am J Hypertens 1990;3:240-41.
- Blood Pres Monit 1999;4:97-101.

- Talking (including listening)
 - > Should be quiet for 5 minutes (especially while BP is measured)
 - ➤ Can increase BP by 10 mmHg¹
- Full bladder
 - ➤ May increase BP by 10 15 mmHg
 - > Ask patient if they need to use the restroom prior to measurement
- Smoking/Alcohol/Caffeine
 - ➤ Increase BP
 - > Should refrain for at least 30 minutes before measurement
- Room temperature
 - Rooms that are too cold increase BP
 - Should be close to ambient temperature
- Dehydration
 - > Decreased blood volume decreases BP

Clothing

- > Tight clothing can be constrictive and increase BP
 - Ideally cuff should be placed on a bare arm (removed from sleeve)
 - Recent evidence suggests that clothing < 2mm thick does not effect BP measurement¹

Wrong Cuff size

- ➤ One of the most common errors in BP measurement²
- ➤ Too small (undercuffing) increases BP & too large (overcuffing) decreases BP³

Cuff Deflation Rate

➤ Deflation rates > 2 mmHg per second can underestimate SBP and overestimate DBP⁴

- 1. Blood Press 2004;13:279-82.
- 2. Circulation 1983;68:763-6.
- 3. Blood Pres Monit 2003;8:101-6.
- Circulation 2005;111:697-716.

Arm Differences

- ➤ Blood pressure differs between arms
 - One study found that 20% of patients had > 10 mmHg difference between arms¹
- ➤ Measure both arms at initial visit and then use higher arm

Observer Error

- ➤ Often termed "terminal digit bias"²
 - Occurs when the observer rounds the last digit to "zero"
 - Also often times rounded to "0 or 5"
 - BP meter measures in increments of 2 mmHg so can't be a "5"
 - 1. J Hypertens 2002;20:1089-95.
 - 2. N Engl J Med 2009;360:e6.

Assessing Blood Pressure

- AHA BP monitoring recommendations
 - Patient should avoid smoking, caffeine, or exercise 30 minutes prior to measurement.
 - Remove clothing from upper arm
 - Sit quietly for 5 minutes
 - Legs uncrossed, back and arm supported
 - Mid-point of cuff even with mid-point of sternum
 - Cuff size determined by arm circumference
 - Lower end of cuff 2-3 cm above antecubital fossa
 - Measure both arms & use the higher reading.
 - An average of 2 to 3 measurements taken on 2 to 3 separate occasions



"Once we finish with your blood pressure, we need to find out why your arm is purple."

AHA Blood Pressure Measurement Recommendations¹

• Preparation:

- Patient should avoid tobacco or caffeinated beverages for 30 minutes prior
- Exam room should be quiet and comfortably warm
- Patient should sit quietly for at least 5 minutes in a chair (with feet on floor)
- Arm should be supported at heart level
- Arm should be free of clothing
- Legs uncrossed, back supported
- Cuff size determined by arm circumference
- Lower end of cuff 2-3 cm above antecubital fossa

Proper Cuff size

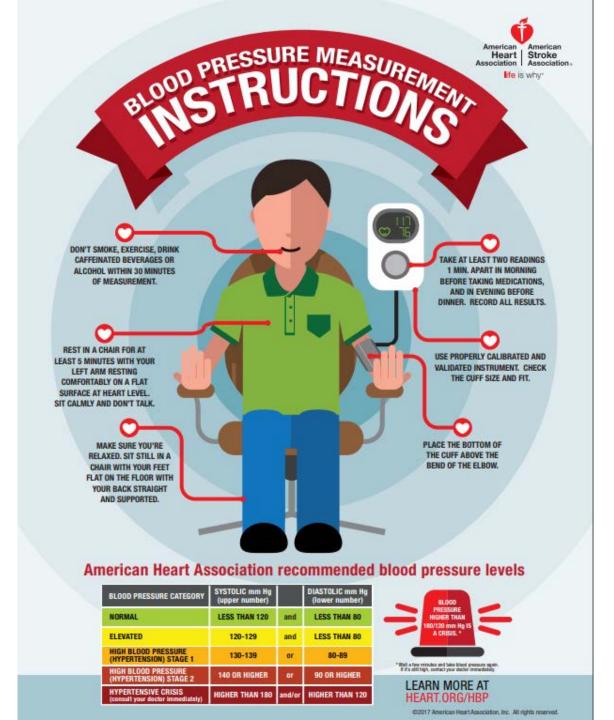
AHA Circumference	AHA Cuff Size
< 24 cm (< 9.5 inches)	Small Adult
24 - 32 cm (9.5 - 12.6 inches)	Standard Adult
33 - 42 cm (13 - 16.5 inches)	Large Adult
> 42 (> 16.5 inches)	Thigh size or XL Adult

Home Blood Pressure Monitoring

- The guidelines also emphasized the importance of home blood pressure monitoring (HBPM)
 - For confirming diagnosis
 - To manage therapy and achieve treatment goals

COR	LOE	Recommendation for Out-of-Office and Self-Monitoring of BP
I	A ^{SR}	Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions.

 Educate patients in the proper method of home blood pressure monitoring



Activities

- Pair up with someone and begin practicing auscultatory method of BP assessment using an appropriate sized cuff and following the AHA methods.
- Assess BP with automated BP monitor and compare results
- Once each person has practiced let one of the instructors know you are ready to assess the BP in the mannequin arm.

SMBP: Device Calibration

- A simple version of the European Society of Hypertension International Protocol has been developed for this purpose and can be done quickly by the health care provider and the patient.¹
- The following steps to ensure accuracy take approximately 10 minutes:
 - Have the patient sit down with his or her arm at heart level. The arm should be completely relaxed.
 - Allow the patient to rest for 5 minutes.
 - Avoid any conversation during the measurements.
 - Take a total of five sequential same-arm blood pressure readings, no more than 30 seconds apart.
 - Have the patient take the first two readings with his or her device.
 - Then the provider takes the third reading, preferably with an aneroid device.
 - Have the patient take the fourth reading.
 - The fifth and final reading is taken by the provider.
 - Compare the difference between the readings from the two cuffs.
 - BP readings will usually decline over the five measurements. The final SBP reading may be as much as 10 mmHg lower than the first.
 - If the difference is < 5 mmHg or less, the comparison is acceptable.
 - If the difference is > 5 mmHg but < 10 mmHg, do the calibration again.
 - If the difference is >10 mmHg, the device may not be accurate.
 - Repeat this procedure annually.

 Centers for Disease Control and Prevention. Self-Measured Blood Pressure Monitoring: Actions Steps for Clinicians. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2014.

SMBP: Resources

- Centers for Disease Control and Prevention. Self-Measured Blood Pressure Monitoring: Action Steps for Public Health Practitioners. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013. Available at: http://millionhearts.hhs.gov/docs/mh_smbp.pdf
- AHA Heart360 program. Available at: https://www.heart360.org/Default.aspx
- AHA. Instructional Video: Monitoring Blood Pressure at Home: <u>http://bit.ly/1pffQBp</u>
- AHA. Printable Log to Record Home Blood Pressure Measurements: <u>http://bit.ly/1sUFssq</u>
- http://effectivehealthcare.ahrq.gov/ehc/products/193/894/smbp cons fin to p ost.pdf
- http://millionhearts.hhs.gov/Docs/MH SMBP Clinicians.pdf